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10/072,425	02/07/2002	Muriel Moser	DECLE55.1C2CD1	4226

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/072,425	MOSER ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,34,35,42,46,50,54 and 58-66* is/are pending in the application.

4a) Of the above claim(s) *58 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,34,35,42,46,50,54,59-63,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed 12/27/07 have been entered.

2. New Claims 58 and 64 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species.

Claims 1, 2, 5-7, 9, 34, 35, 42, 46, 50, 54, 59-63, 65, and 66 read on the elected invention and are being acted upon.

3. In view of the instant amendment, the previous rejections under the first and second paragraphs of 35 U.S.C. 112 have been withdrawn. Regarding rejections for inadequate written description due to the introduction of new matter into the claims, all rejections have been combined into new rejections below. Additionally, the rejection of Claims 13, 14, 23, and 24 under 35 U.S.C. 103(a) as being unpatentable over Guo et al. in view of Sornasse et al., Young et al., and Reid et al. has been withdrawn in view of the cancellation of the claims.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 5-7, 9, 34, 35, 50, 54, 59-63, 65, and 66 stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990).

As set forth previously, Guo et al. teaches a method for producing a plurality of hybrids/hybridomas comprising a bone marrow derived antigen-presenting B cell and a tumor cell (see particularly page 520, columns 2-3, 11.). The method comprises the providing of a tumor sample and an isolated autologous B cell, and the fusing of the cells with PEG to produce a plurality of hybrids/hybridomas (see particularly page 518, column 2). The reference teaches that the hybrids/hybridomas comprise cells that express both tumor-specific antigens and the machinery for antigen presentation, i.e., characteristics of both tumor cells and B cell APCs (see particularly page 518, column 1), that said

hybrids/hybridomas are useful for the induction of an anti-tumor response in that they reduce the number of tumor cells upon administration to a subject (see particularly page 518, column 3). The reference further teaches that the hybrids/hybridomas were selected on the basis of a tumor cell surface marker and a B cell surface marker (see particularly page 518, column 3).

The reference teaching differs from the claimed invention only in that it does not teach the use of a DC as the antigen presenting component of the hybrid nor the isolation of said DCs from blood.

Sornasse et al. teaches that, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo* (see particularly pages 16-17, Results). The reference teaches the superiority of DCs over B cells for *in vivo* use, "Our data emphasize the main role of DC in initiating primary responses *in vivo*" (see page 18, column 1). Note that the DCs of the reference comprise splenic DCs which would include bone marrow derived DCs, lymphoid DCs, and myeloid DCs.

Young et al. teaches the routine isolation of DCs from human PBMC (peripheral blood mononuclear cells) (see page 1316, *PBMC and Preparation of Leukocyte Subpopulations*)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., by the method of Guo et al., substituting a DC for the B cell in said hybrids/hybridomas, as taught by Sornasse et al, said DCs being isolated from human blood, as taught by Young et al. One of ordinary skill in the art at the time of the invention would have been motivated to make said substitution because, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo*, as taught by Sornasse et al. "Our data emphasize the main role of DC in initiating primary responses *in vivo*". Note that the additional limitations such as preparing a primary cell culture of the tumor cells comprises only an obvious and necessary step when said culture is not readily available as it was for Guo et al. Note, however, the BERH-2 tumor cells of Guo et al. derive from a hepatocarcinoma thus, said cells were previously the "primary culture" of tumor cells as set forth in the claims. Finally note that Young et al. teaches the routine use of human blood as a convenient source of DCs.

Applicant's arguments, filed 12/27/07, have been fully considered but they are not persuasive. Applicant argues surprising results and a lack of predictability in producing a functional DC/tumor hybrid. Applicant cites the Agency's obviousness guidelines. Applicant further provides and cites Unternaehrer et al. (2007).

As set forth previously, Guo et al. teaches that B cell hybrids retain the characteristics of the APC fusion partner, e.g., the B cell. Likewise, the ordinarily skilled artisan would expect DC hybrids to retain the APC characteristics of the DC as well. While Applicant goes to some lengths, including italicizing, underlining, and italicizing and underlining, in urging that DC hybridomas would be unpredictable, it is unclear

precisely what aspects of the now 33+ year old hybridoma technology, first described by Köhler and Milstein in 1975, Applicant is alleging are unpredictable in the instant context. Indeed, the specification discloses that the Inventors simply "adapted" a method set forth by Franssen et al. in 1982 (page 33). There is no disclosure of unpredictability in said adaptation. Further, the specification discloses that it would be routine to employ "analogous procedures and techniques" disclosed in the specification in murine systems to humans (page 22). Again, there is no disclosure of unpredictability nor that the claimed invention requires any other than routine and well-known techniques.

Regarding the Agency's obviousness guidelines, the "Rationales" discussed by Applicant are actually set forth in MPEP 2143 as "EXEMPLARY RATIONALES". The MPEP goes on to state that "the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel".

Regarding Unternaehrer et al. (2007), it is unclear how the reference supports Applicant's arguments. As Applicant states, the reference teaches that DCs have "superior antigen presenting ability" in comparison to B blasts. There is no teaching in the reference that a DC/tumor hybrid would be expected to lose this superior ability.

Applicant argues "in view of the fact that at the time of the invention, to Applicant's knowledge no dendritic cell/tumor hybrids had been reported as retaining the physiological activity of the dendritic cell required by the instant claims, indicates that the ordinary skilled artisan could not predict that the dendritic cell/tumor hybrid produced by the instantly claimed methods would retain the recited antigen presenting cell physiological activities attributed to the dendritic cell".

As set forth previously, Peters 1980 and 1981, both of record, teach the routine fusion of DCs to tumor cells. The resulting hybrids were capable of activating T lymphocytes. As set forth in the 1980 reference, adherent, esterase-positive, nonphagocytic cells were DCs. After the routine fusion of the DCs to tumor cells the resulting hybrids displayed the capacity to induce T cell growth and at least one of the hybrids stained positive with anti-Ia (MHC Class II), i.e., the resulting

hybrids displayed both the activity and the surface identity of mature DCs.

In sum then, there is no evidence of record supporting Applicant's allegations of unpredictability and Applicant's assertions of unexpected results. Accordingly the rejection has been maintained.

6. Claims 2, 42, and 46, stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990), as applied to Claims 1, 5-7, 9, 34, 35, 50, 54, 59-63, 65, and 66 above, and in further view of U.S. Patent No. 5,851,756.

As set forth previously, Guo et al., Sornasse et al., and Young et al. have been discussed, supra. The references differ from the claimed invention in that they do not teach the induction of DC characteristics before using said hybrids/hybridomas, nor the induction of said characteristics using GM-CSF.

The '756 patent teaches the induction of DC characteristics using GM-CSF (see particularly Example I). The reference further teaches that DC exist in relatively small numbers in blood, thus the induction of DC (and thus, DC characteristics) in GM-CSF before use provides a method to increase the number of said DCs (see particularly column 4, line 63 - column 5, line 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., Sornasse et al., and Young et al., by the method of Guo et al., substituting a DC induced with GM-CSF before use, as taught by the '756 patent, for the B cell in said hybrids/hybridomas. One of ordinary skill in the art at the time of the invention would have been motivated to induce DC (and thus, DC characteristics) with GM-CSF before use because DC exist in relatively small numbers in blood, thus the induction of DC in GM-CSF before use provides a method to increase the number of said DCs, as taught by the '756 patent.

See the Examiner's response to Applicant's arguments above.

7. Claims 50 and 54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990), as applied to Claims 1, 5-7, 9, 34, 35, 50, 54, 59-63, 65, and 66 above, and in further view of U.S. Patent No. 5,637,483.

As set forth previously, Guo et al., Sornasse et al., and Young et al. have been discussed, supra. The references differ from the claimed invention in that they do not teach the treatment of the hybrids/hybridomas with irradiation before using to prevent proliferation.

The '483 patent teaches the treatment of a tumor cell-containing anti-tumor vaccine with irradiation before using to prevent proliferation (see particularly column 3, lines 65-67 and column 14, lines 3-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., Sornasse et al., and Young et al., by the method of Guo et al. and employ irradiation before using, as taught by the '483 patent. One of ordinary skill in the art at the time of the invention would have been motivated to treat the hybrids/hybridomas with irradiation before using to prevent proliferation, as taught by the '483 patent.

See the Examiner's response to Applicant's arguments above.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 7, 9, 10, 59, 60, and 66 stand/are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Breel et al. (1988, IDS).

As set forth previously, Breel et al. teaches a method of producing a plurality of DC/tumor cell hybrids comprising providing a sample of tumor (SP2/0 myeloma cells, necessarily obtained from cell culture), providing isolated autologous (all cells are autologous to their source) lymph node DCs, and fusing the DCs with the tumor cells by a standard hybridoma fusion protocol (which would include PEG fusion and HAT selection) to produce a plurality of hybrids (see particularly Materials and Methods, page 168). The reference further teaches the selecting of a hybrid which exhibits a DC cell surface marker (NLDC-145) (see particularly Results, page 170). Note that the recitation of "providing a sample of a tumor *against which a response is needed*" is not considered to comprise an actual method step. The recitation of producing … cell hybrids *which induce an anti-tumor response when provided to a patient causing a reduction of the number of tumor cells in said patient*" is considered to be an inherent property of the hybrids.

Applicant's arguments, filed 12/27/07, have been fully considered but they are not persuasive. Applicant argues that the reference does not teach that the hybrids of the claims have the required ability to induce an anti-tumor response when provided to a patient.

There are only two possibilities regarding the hybrids of Breel et al., either they have the claimed ability, or they do not. If as Applicant argues, the claimed ability of being

capable of activating naïve T cells is actually so unpredictable that the cited prior art does not apply, then Applicant's claims by necessity must be limited to the embodiments in which the unpredictable invention has been shown to function. That is, Applicant's invention must be limited to the production of the HY41 and HY62 hybrids capable of inducing an anti-tumor response to P815 cells in mouse models. If, as Applicant argues, the invention is so unpredictable, then clearly broad claims that would encompass human hybrids cannot be allowed because there is no demonstration in the instant specification that they would function as claimed. On the other hand, if the production of DC/tumor hybrids is as routine as the specification discloses, and the capabilities of said hybrids is so predictable as to not require a showing of said capabilities, then the broad claims of the instant application are enabled and the prior art does apply, including Breel et al.

Applicant simply cannot persuasively argue "both sides", i.e., that the methods of the prior art are so unpredictable as to require the withdrawal of all rejections, but that the broad methods of the instant claims are so predictable as to allow for the enablement of methods that would encompass the use of human cells for which there is no *in vivo* showing in the instant specification of any anti-tumor efficacy.

10. The following are new grounds for rejection. Note that for efficiency the multiple rejections for the introduction of new matter into the claims have been combined.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 2, 5-7, 9, 34, 35, 42, 46, 50, 54, 59-63, 65, and 66 stand/are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a rejection for inadequate

written description due to the introduction of new matter into the claims.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of:

A) The method of Claim 1 comprising producing a plurality of DC/tumor cell hybrids:

a) for "a reduction of the number of tumor cells in a patient",

b) comprising the "allogeneneic" DCs of step (a),

c) comprising the "allogeneic tumor cell characteristic of the same cancer type with respect to said patient" of step (b),

d) comprising selecting hybrids "that exhibit DC markers, TAAs and the capacity to activate naïve T cells in vitro that can recognize the cancer cells of step (b)".

B) The method of Claim 9 comprising producing a fused cell product "using PEG".

C) The method of Claim 34 comprising "tumor cells … sensitive to a drug".

D) The method of Claim 59 comprising "a tumor cell line having at least one TAA in common with said tumor sample".

E) The method of Claim 65 comprising "an allogeneic tumor cell with respect to the patient, and has one or more TAAs in common with that of said autologous tumor cell".

E) The method of Claim 66.

Note that Applicant has curiously provided arguments regarding previous rejections necessitated by previous amendments to claims that are now canceled, but has failed to provide support for the newly submitted limitations and claims. Arguments addressing cancelled claims will not be addressed. Arguments addressing still pending limitations will be addressed here.

Regarding A), a), Applicant cites original Claim 1 and again cites pages 15 and 60 of the specification. The disclosure of pages 15 and 60 has been addressed previously, see the Final Office action of 9/08/05. While original Claim 1 did

recite the limitation necessitating the rejection set forth above, original Claim 1 is not "original" to parent applications 09/951,849 nor 09/049,502, of which the instant application claims to be a Divisional application and a Continuation application, respectively. Thus, the limitations of the claim must find support in the specification common to the three applications or the instant application must be filed as a Continuation-In-Part (CIP). As support for the limitation has not been found, and the instant application has not been filed as a CIP, the limitation is considered to comprise the introduction of new matter into the claims.

Regarding B), Applicant cites original Claim 9 and again cites Examples 3, 9, and 12 of the specification. Examples 3, 9, and 12 have been addressed previously, see the Final Office action of 9/08/05. Regarding the citing of original Claim 9, the same issue set forth in the previous paragraph applies to this limitation.

Regarding the limitations of C) - E), they have not been found in the instant specification.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 34 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, specifically:

A) The "tumor cells" of Claim 34 have no antecedent basis in step (a) of Claim 1.

B) Claim 63 is a duplicate of Claim 62.

15. No claim is allowed.

16. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

19. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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